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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,768	12/02/1998	JEFFRY D. WATKINS	P-IX-2947	4594

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EXAMINER

HELMS, LARRY RONALD

ART UNIT PAPER NUMBER

1642

DATE MAILED: 06/20/2002

24

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/203,768

Applicant(s)

WATKINS ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-48 is/are pending in the application.
- 4a) Of the above claim(s) 7-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 47 and 48 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

**DETAILED ACTION**

***Request for Continued Examination***

1. The request filed on 4/5/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/203768 is acceptable and a RCE has been established. Claims 1-6, 47-48 are currently under prosecution. An action on the RCE follows.
2. Claims 1-48 are pending.  
Claims 1 and 6 have been amended.
3. Claims 7-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 9.
4. Claims 1-6 and 47-48 are under examination.
5. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.
6. The following Office Action contains some NEW GROUNDS of rejection.
7. **NOTE:**  
The following papers have not been made part of the permanent records of the United States Patent and Trademark Office (Office) for this application (37 CFR 1.52(a)) because of damage from the United States Postal Service irradiation process:

Mailroom Stamp Date

Certificate of Mailing Date

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\_\_\_\_ 4/15/02 \_\_\_\_\_

\_\_\_\_ 4/5/02 \_\_\_\_\_

\_\_\_\_ 4/22/02 \_\_\_\_\_

\_\_\_\_ 4/9/02 \_\_\_\_\_

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\_\_\_\_\_

The above-identified papers, however, were not so damaged as to preclude the USPTO from making a legible copy of such papers. Therefore, the Office has made a copy of these papers, substituted them for the originals in the file, and stamped that copy:

COPY OF PAPERS  
ORIGINALLY FILED

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If applicant wants to review the accuracy of the Office's copy of such papers, applicant may either inspect the application (37 CFR 1.14(d)) or may request a copy of the Office's records of such papers (*i.e.*, a copy of the copy made by the Office) from the Office of Public Records for the fee specified in 37 CFR 1.19(b)(4). Please do **not** call the Technology Center's Customer Service Center to inquiry about the completeness or accuracy of Office's copy of the above-identified papers, as the Technology Center's Customer Service Center will **not** be able to provide this service.

If applicant does not consider the Office's copy of such papers to be accurate, applicant must provide a copy of the above-identified papers (except for any U.S. or foreign patent documents submitted with the above-identified papers) with a statement that

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such copy is a complete and accurate copy of the originally submitted documents. If applicant provides such a copy of the above-identified papers and statement within **THREE MONTHS** of the mail date of this Office action, the Office will add the original mailroom date and use the copy provided by applicant as the permanent Office record of the above-identified papers in place of the copy made by the Office. Otherwise, the Office's copy will be used as the permanent Office record of the above-identified papers (*i.e.*, the Office will use the copy of the above-identified papers made by the Office for examination and all other purposes). This three-month period is not extendable.

***Rejections Withdrawn***

8. The rejection of claims 1-6 and claims 47-48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1-4, 6 and 47-48 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

***Response to Arguments***

10. The rejection of claim 5 under 35 U.S.C. 112, first paragraph, is maintained and made again.

The response filed 4/5/02 has been carefully considered but is deemed not to be persuasive. The response did not address this part of the rejection. In response to this argument, the rejection is reiterated.

The claim as written as drawn to pharmaceutical compositions which read on in vivo treatment for cancer. However, the data presented to support the enablement of the claim is based on cell culture, in vitro studies.

One cannot extrapolate the teaching of the specification to the claimed invention because the *in vitro* experimental data presented is clearly not drawn to subjects with tumor cells. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to

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thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that.

The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years.

Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that the *in vitro* environment would correlate with the *in vivo* environment.

Further, One cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of LCD, related coal tar compositions, analogues or derivative thereof would function as claimed based only upon the known mechanism of action of NADPH. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that

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tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3 ). The disclosed intended use for the claimed pharmaceutical composition is for the treatment of cancer". The specification does not enable in vivo administration of the antibody for cancer treatment. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed antibodies with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

***The following are some NEW GROUNDS of rejections***

***Claim Rejections - 35 USC § 112***

11. Claims 1-4 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human monoclonal antibody or antigen binding fragment thereof comprising SEQ ID NO:2 and SEQ ID NO:4 or a human monoclonal antibody or antigen binding fragment thereof having conservative substitutions in SEQ ID NO:2 and 4 wherein the antibody binds the same antigen as the monoclonal antibody comprising SEQ ID NO:2 and 4, does not reasonably provide enablement for any monoclonal antibody or antigen binding fragment thereof having any conservative substitutions in SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody

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binds just any neoplastic cell or antigen thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any antibody with any conservative substitutions in SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds to any neoplastic cell or antigen thereof.

The specification teaches an antibody comprising SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds the LH11238 antigen. The specification teaches conservative substitutions in the antibody such that the antibody maintains its function of selectively binding a tumor specific antigen (see page 8, lines 11-16) which means in this instance the LH11238 antigen. The specification does not enable any antibody with conservative substitutions that binds to just any neoplastic cell or any antigen thereof.

The claims encompass any antibody with any conservative changes in SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds any neoplastic cell or antigen. The claims are not commensurate in scope with the enablement provided in the

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specification. The claims encompass any conservative changes in the antibody wherein it is known in the art that changes in amino acid sequences have a profound effect on function. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, PTO 892, Attach to No11). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain any conservative substitution, have the required binding function to the same antigen as that which the antibody having SEQ ID NO:2 and 4 binds. In addition, Colman (Research in Immunology 145:33-36, 1994) teach that "The above examples paint a confusing picture of the specificity of antibody-antigen interaction. In one structural context, a very conservative substitution may abolish binding; in another, a nonconservative substitution may have very little effect on the binding" (see page 35, left column). Thus, while it may be true that one can make an antibody with conservative substitutions, it would require undue experimentation to predict which substitutions would produce an antibody that would retain binding to just any neoplastic cell or antigen thereof except the same antigen as that bound by the antibody of SEQ ID NO:2 and 4. In other words the claims broadly read on changing the amino acid sequence of SEQ ID NO:2 and 4 such that it can bind any neoplastic cell or antigen thereof, however, the specification does not enable such changes that result in the antibody binding to just any neoplastic cell or antigen.

Therefore, undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

### ***Conclusions***

12. No Claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

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Respectfully,

Larry R. Helms Ph.D.

703-306-5879

*Sheela Huff*  
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PRIMARY EXAMINER